APPENDIX E

TARGET ANALYTE DOSE-RESPONSE VARIABLES AND ASSOCIATED INFORMATION

Table E-1. Target Analyte Dose-Response Variables and Associated Information

	Noncarcinogens		Carcinogens		
Target analyte	RfD[a] (degree of confidence; uncertainty factor)	Critical toxic effect	SF[b] (discussion of confidence)	Critical carcinogenic effect[c]	EPA carcinogenicity classification[d]
Metals					
Arsenic (inorganic)	3×10^{-4} [e] (medium; 3)	Hyperpigmentation, keratosis and possible vascular complications in humans	NA[f]	—	A[e]
Cadmium	1×10^{-3} (high; 10)	Significant proteinurea in humans	NA	—	B1[g]
Mercury (as methylmercury)	3×10^{-4} [h] (medium; 10)	Central nervous system effects (e.g., ataxia, parathesia) in humans	NA	—	C
	1×10^{-4} [e,h] (medium; 10)	Developmental neurological abnormalities in human infants.			
Selenium[i]	5×10^{-3} (high; 3)	Selenosis in humans	NA	—	D
Tributyltin	3×10^{-5} [e] (low; 1000)	Immunotoxicity in rats	NA	—	NA[e]

See notes and references at end of table.

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Table E-1 (continued)

Target analyte	Noncarcinogens: RfD[a] (degree of confidence; uncertainty factor)	Noncarcinogens: Critical toxic effect	Carcinogens: SF[b] (discussion of confidence)	Carcinogens: Critical carcinogenic effect[c]	Carcinogens: EPA carcinogenicity classification[d]
Organochlorine Pesticides					
Chlordane (sum of cis- and trans-chlordane, cis- and trans-nonachlor, and oxychlordane)	6×10^{-5} (low; 1000)	Regional liver lesions (hypertrophy) in one strain of female rats	1.3 (Adequate number of animals observed. SF is the geometric mean of SFs for four data sets from two studies. This SF is consistent with SF = 1.1 derived from less sensitive rat species.)	Hepatocellular carcinomas in two strains of mice (male and female)	B2
DDT (sum of 4,4'- and 2,4'- isomers of DDT, DDE, and DDD)	5×10^{-4} (medium; 100)	Liver lesions in rats	3.4×10^{-1} (SF is geometric mean of SFs from 10 data sets. SF from mouse data only = 4.8×10^{-1}; SF from rat data only = 1.5×10^{-1}.)	DDT: Liver tumors in six studies in two mouse strains and two studies in two rat strains	B2

See notes and references at end of table.

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Table E-1 (continued)

Target analyte	Noncarcinogens: RfD[a] (degree of confidence; uncertainty factor)	Noncarcinogens: Critical toxic effect	Carcinogens: SF[b] (discussion of confidence)	Carcinogens: Critical carcinogenic effect[c]	Carcinogens: EPA carcinogenicity classification[d]
			3.4×10^{-1} (Adequate number of animals observed. SF for mouse studies alone is within a factor of 2 for mouse and hamster data combined.)	DDE: Liver tumors (including carcinomas) in two strains of mice and in hamsters	B2
			2.4×10^{-1} (Adequate number of animals observed. SF calculated using tumor incidence data from only one dose.)	DDD: Liver tumors in one strain of mice (males only)	B2
Dicofol	1×10^{-3} [j] (NA, 1000)	Increase liver to body weight ratios observed in 2-yr rat feeding study.[j]	NA	—	C[k]
Dieldrin	5×10^{-5} (medium; 100)	Liver lesions (focal proliferation and focal hyperplasia) in one strain of female rats	16 (SF is the geometric mean of SFs from 13 data sets. Individual SFs ranged within a factor of 8.)	Liver carcinomas in five strains of mice (male and female)	B2
Endosulfan (sum of endosulfan I and II)	6×10^{-3} [l] (medium; 100)	Decreased body weight gain and progressive glomerulonephrosis and blood vessel aneurysmsin one strain of male rats[l]	NA	—	E[k]

See notes and references at end of table.

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Table E-1 (continued)

Target analyte	Noncarcinogens: RfD[a] (degree of confidence; uncertainty factor)	Noncarcinogens: Critical toxic effect	Carcinogens: SF[b] (discussion of confidence)	Carcinogens: Critical carcinogenic effect[c]	Carcinogens: EPA carcinogenicity classification[d]
Endrin	3×10^{-4} (medium; 100)	Mild histological lesions in livers in dogs (both sexes)	NA	—	D
Heptachlor epoxide	1.3×10^{-5} (low; 1000)	Increased liver-to-body weight ratios in male and female dogs	9.1 (Adequate number of animals observed in both studies, but survival in one study was low. This SF is consistent with SF = 5.8 for one strain of seven rats.)	Hepatocellular carcinomas in two strains of mice (male and female)	B2
Hexachlorobenzene	8×10^{-4} (medium; 100)	Liver effects (hepatic centrilobular basophilic chromogenesis) in one strain of rats (both sexes)	1.6 (Significant increases in malignant tumors observed among an adequate number of animals observed for their lifetime.)	Hepatocellular carcinomas in one strain of rats (females only)	B2
Lindane (γ-BHC)	3×10^{-4} (medium; 1000)	Liver and kidney toxicity (liver hypertrophy, kidney tubular degeneration, hyaline droplets, tubular distension, interstitial nephritis, and basiophilic tubules) in both sexes of one strain of rats	1.3[m]	—	B2/C[k,n]

See notes and references at end of table.

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Table E-1 (continued)

Target analyte	Noncarcinogens: RfD[a] (degree of confidence; uncertainty factor)	Noncarcinogens: Critical toxic effect	Carcinogens: SF[b] (discussion of confidence)	Carcinogens: Critical carcinogenic effect[c]	Carcinogens: EPA carcinogenicity classification[d]
Mirex	2×10^{-4} (high; 300)	Liver cytomegaly, fatty metamorphosis, angiectasis and thyroid cystic follicles in one strain of rats.	NA[o]	—	R
Toxaphene	2.5×10^{-4} [j,p] (NA, 1000)	Slight liver degeneration—granularity and vacuolization of hepatocytes.[j]	1.1 (Adequate number of animals observed. A dose-response effect was seen in a study with three non-zero dose levels.)	Hepatocellular carcinomas and neoplastic nodules in one strain of mice (males only)	B2
Organophosphate Pesticides					
Chlorpyrifos	3×10^{-3} (medium, 10)	Decreased plasma ChE activity observed in 20-day human feeding study.	NA	—	D[k]
Diazinon	9×10^{-5} [j] (NA, 100)	Inhibition of plasma ChE observed in 90-day rat feeding study.[j]	NA	—	D[k]
Disulfoton	4×10^{-5} (medium, 1000)	ChE inhibition and degeneration of the optic nerve observed in 2-yr dog feeding study.	NA	—	D[k]

See notes and references at end of table.

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Table E-1 (continued)

Target analyte	Noncarcinogens: RfD[a] (degree of confidence; uncertainty factor)	Noncarcinogens: Critical toxic effect	Carcinogens: SF[b] (discussion of confidence)	Carcinogens: Critical carcinogenic effect[c]	Carcinogens: EPA carcinogenicity classification[d]
Ethion	5×10^{-4} (medium, 100)	Plasma ChE inhibition and inhibition of brain ChE observed in 21-day human feeding study.	NA	—	D[k]
Terbufos	1.3×10^{-4} [j] (NA, 10)	Inhibition of plasma ChE observed in 28-day dog feeding study.[j]	NA	—	D[k]
Chlorophenoxy Herbicides					
Oxyfluorfen	3×10^{-3} (high, 100)	Increased absolute liver weight and nonneoplastic lesions observed in 20-month mouse feeding study.	1.3×10^{-1} [k]	Evidence of carcinogenicity (liver tumors) in mice.	C[k]
PAHs[q]					
Benzo[*a*]pyrene	NA	—	7.3[e] (Data less than optimal, but acceptable. Four data sets used from two different studies using two different species (rats and mice; both sexes) to derive geometric mean of four calculated slope factors.)	Squamous cell carcinoma of the forestomach in one strain of mice (both sexes). Forestomach, larynx, and esophagus papillomas and carcinomas in one strain of rats (both sexes)	B2

See notes and references at end of table.

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Table E-1 (continued)

Target analyte	Noncarcinogens: RfD[a] (degree of confidence; uncertainty factor)	Noncarcinogens: Critical toxic effect	Carcinogens: SF[b] (discussion of confidence)	Carcinogens: Critical carcinogenic effect[c]	Carcinogens: EPA carcinogenicity classification[d]
PCBs					
Total PCBs (sum of Aroclors)	2×10^{-5} [e,r] (medium; 300)	Ocular exudate, inflamed, prominent Meibomian glands, distorted growth of finger and toe nails, decreased antibody response to sheep erythrocytes in monkey clinical and immunologic studies	7.7[s] (Adequate number of animals observed for their normal lifespan. Only one non-zero test dose used.)	Trabecular carcinomas/adenocarcino-mas, neoplastic nodules in one strain of rats (females only)	B2
	7×10^{-5} [e,t] (medium; 100)	Reduced birth weights in monkeys			
Dioxins/furans	NA	—	1.56×10^{5} [u]	NA	B2

NA = Not available in IRIS (1992).
PAHs = Polycyclic aromatic hydrocarbons.
PCBs = Polychlorinated biphenyls.

[a] RfD = Oral reference dose (mg/kg/day); from IRIS (1992) unless otherwise noted (see Section 5.1.1).

[b] SF = Oral slope factor $(mg/kg/day)^{-1}$; from IRIS (1992) unless otherwise noted (see Section 5.1.2).

[c] The critical effect is the effect observed in oral dose response studies used to determine the SF.

[d] Except where noted, all EPA carcinogenicity classifications are taken from IRIS (1992):
- A = Human carcinogen based on sufficient evidence from epidemiologic studies.
- B1 = Probable human carcinogen based on at least limited evidence of carcinogenicity to humans.
- B2 = Probable human carcinogen based on a combination of sufficient evidence in animals and inadequate data in humans.
- C = Possible human carcinogen based on limited evidence of carcinogenicity in animals in the absence of human data.
- D = Not classifiable based on lack of data or inadequate evidence of carcinogenicity from animal data.

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E = No evidence of carcinogenicity for humans (no evidence of carcinogenicity in at least two adequate animal tests in different species or in both epidemiologic and animal studies).
R = Currently under review by EPA.

[e] From IRIS (1995).

[f] The SF for inorganic arsenic is currently under review by the Agency. At this time, EPA does not have a cancer SF to recommend for use in conducting fish consumption risk assessments.

[g] Based on limited evidence from human occupational epidemiologic studies where the primary route of exposure was by inhalation, and on sufficient evidence from studies in which rats and mice were exposed by inhalation and intramuscular and subcutaneous injection. However, data are inadequate to conclude that cadmium is carcinogenic via ingestion. The EPA Office of Drinking Water classifies cadmium as a Group D carcinogen in the health advisory for cadmium (U.S. EPA, 1987).

[h] The EPA has recently reevaluated the RfD for methylmercury, primarily because of concern about evidence that the fetus is at increased risk of adverse neurological effects from exposure to methylmercury (Marsh et al., 1987; Piotrowski and Inskip, 1981; Seafood Safety, 1991; WHO, 1976, 1990). On May 1, 1995, IRIS was updated to include an oral RfD of $1x10^{-4}$ mg/kg/d based on developmental neurological effects in human infants. An oral RfD of $3x10^{-4}$ mg/kg/d for chronic systemic effects of methylmercury among the general adult population was available in IRIS until May 1, 1995; however, it was not listed in the IRIS update on that date. For the purposes of calculating an SV for methylmercury that is protective of developing fetuses and nursing infants, the EPA Office of Water has chosen to continue to use the general adult population RfD of $3x10^{-4}$ mg/kg/d for chronic systemic effects of methylmercury until a value is relisted in IRIS, and to reduce this value by a factor of 5 to derive an RfD of $6x10^{-5}$ mg/kg/d for developmental effects among fetuses and nursing infants. The protective factor of 5 is based on experimental results that suggest a possible fivefold increase in fetal sensitivity to methylmercury exposure. This more protective approach recommended by the EPA Office of Water was deemed to be most prudent at this time. This approach should be considered interim until such time as the Agency has reviewed new studies on the chronic and developmental effects of methylmercury.

[i] The oral RfD is for selenious acid (IRIS, 1992). The evidence of carcinogenicity for various selenium compounds in animals and mutagenicity studies is conflicting and difficult to interpret. However, evidence for selenium sulfides is sufficient for a B2 classification (IRIS, 1992).

[j] Reference dose information is taken from the Office of Pesticide Programs Reference Dose Tracking Report (U.S. EPA, 1993).

[k] EPA carcinogenicity classification taken from Classification List of Chemicals Evaluated for Carcinogenicity Potential (U.S. EPA, 1992a).

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[l] Reference dose information is taken from the Office of Pesticide Programs Reference Dose Tracking Report (U.S. EPA, 1995).

[m] IRIS (1992) has not provided an SF for lindane. The SF value listed for lindane was calculated from the water quality criteria (0.063 µg/L) (U.S. EPA, 1992d) and is comparable to the SF of 1.33 mg/kg/d^{-1} from the Public Health Risk Evaluation Database (U.S. EPA, 1988b).

[n] Previously classified by EPA as B2 (IRIS, 1989). Available data need to be reviewed further, but at a minimum lindane will be classified as a C carcinogen (U.S. EPA, 1992a).

[o] The National Study of Chemical Residues in Fish (U.S. EPA, 1992b, 1992c) used a value of SF = 1.8 for mirex from HEAST (1989).

[p] The RfD value is the Office of Pesticide Programs value; this value was never submitted for verification.

[q] This RfD is for benzo[*a*]pyrene (IRIS, 1995). There are no other RfDs or SFs listed for PAHs in IRIS (1995). It is recommended that, in both screening and intensive studies, tissue samples be analyzed for benzo[*a*]pyrene, benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, chrysene, dibenz[*a,h*]anthracene, and indeno*[1,2,3-cd*]pyrene, and that the relative potencies given for these PAHs in the EPA provisional guidance for quantitative risk assessment of PAHs (U.S. EPA, 1993c) be used to calculate a potency equivalency concentration (PEC) for each sample for comparison with the recommended SV for benzo[*a*]pyrene (see Section 5.3.2.3). At this time, EPA's recommendation for risk assessment of PAHs (U.S. EPA, 1993c) is considered provisional because quantitative risk assessment data are not available for all PAHs. This approach is under Agency review and over the next year will be evaluated as new health effects benchmark values are developed. Therefore, the method provided in this guidance document is subject to change pending results of the Agency's reevaluation.

[r] This RfD for PCBs is based on the chronic toxicity of Aroclor 1254 (IRIS, 1995).

[s] This SF is based on a carcinogenicity assessment of Aroclor 1260. The SF of Aroclor 1260 is intended to represent the upper bound risk for all PCB mixtures (IRIS, 1992). **Note:** EPA is currently reevaluating the SF for PCBs and a revised value may be available for comment in the Fall of 1995.

[t] This RfD for PCBs is based on the developmental toxicity of Aroclor 1016 (IRIS, 1995).

[u] The SF value listed is for 2,3,7,8-tetrachlorodibenzo-p-dioxin 2,3,7,8-TCDD (U.S. EPA, 1986). The National Study of Chemical Residues in Fish used a value of RfD = $1x10^{-9}$ for 2,3,7,8-TCDD from ATSDR (1987). It is recommended that, in both screening and intensive studies, the tetra- through octa-chlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) be determined and a toxicity-weighted total concentration be calculated for each sample for comparison with the recommended SV, using the revised interim method for estimating Toxicity Equivalency Concentration (TECs) (Barnes and Bellin, 1989; U.S. EPA, 1991). If resources are limited, the 2,3,7,8-TCDD and 2,3,7,8-TCDF congeners should be determined, at a minimum.

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